

Please substitute the enclosed sections entitled "5.3 EXAMPLE 3 – DEVELOPMENT AND TESTING OF RIBOZYME TARGETING A_{2B} ADENOSINE RECEPTOR mRNA" for the corresponding section originally submitted with the application as filed.

Please substitute the enclosed TABLE 4, TABLE 5 and TABLE 6 for the corresponding tables originally submitted with the application as filed.

After page 111, please insert the Sequence Listing that is enclosed herewith.

REMARKS

The above amendments are for the purpose of correcting the drawing descriptions, correcting some of the tables, and inserting the sequence listing.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4300.014100.

Please date stamp and return the accompanying postcard to evidence receipt of these documents.

Respectfully submitted,



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3. BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements, and in which:

FIG. 1 shows adenosine, acting through its type A₂ receptor, can act to increase oxygen supply via two paths. During acute hypoxia, adenosine acts on smooth muscle cells, resulting in vasodilation (A_{2A}). With chronic ischemia, adenosine acts as an angiogenic agent by exerting a mitogenic effect on microvascular endothelial cells (in HREC, A_{2B}; see below). It is this latter effect that can be interfered with in an attempt to develop a pharmacological therapy for neovascular diseases. A distinct receptor subtype that mediates solely the mitogenic effect of adenosine would allow the targeting of a selective antagonist against that receptor subtype, without preventing the vasodilation mediated by the A_{2A} receptor;

FIG. 2A shows HREC proliferation after stimulation with NECA alone or in combination with a blocking antibody to VEGF. Open bars are results after 24 hr of exposure; filled bars are results after 48 hr. (*), significantly different from 10 μ M NECA alone for the respective exposure time by ANOVA ($p < 0.05$). Also shown are control cells exposed to VEGF alone or in combination with anti-VEGF to demonstrate the efficacy of the antibody;

FIG. 2B shows VEGF content in conditioned medium from HREC after stimulation with NECA in the presence or absence of sense or antisense oligonucleotides homologous to human A_{2B} adenosine receptor or to human VEGF. Assay duration was 48 hr. A_{2B} antisense treatment reduces the amount of VEGF protein secreted in response to NECA to levels equaling or exceeding the reduction evident by VEGF antisense treatment;

FIG. 3A and **FIG. 3B** show NECA, at the concentrations indicated in the legends, induces a transient activation of ERK/MAPK in HREC that peaks at 5 min and desensitizes by 20 min after exposure. HREC were serum-starved for 24 hr and pre-treated for 20 min with 1 U/mL adenosine deaminase prior to adding NECA. Activated ERK/MAPK was visualized on Western blots by enhanced chemiluminescence using EC10 monoclonal antibody;

FIG. 4A, **FIG. 4B** and **FIG. 4C** show the A₁-selective agonist CPA stimulates ERK/MAPK phosphorylation in HREC, however the A_{2A}-selective agonist CGS did not activate ERK/MAPK;

5 **FIG. 5** shows HREC were pretreated for 30 min with the MEK inhibitor PD98059 or the PKA inhibitor H-89 and stimulated with NECA for 5 min. PD98059 inhibited ERK activation, while H-89 increased basal ERK activation. H-89 did not block NECA-stimulated ERK activation, suggesting that PKA is not involved in signaling from the adenosine receptor to ERK. The non-selective adenosine receptor antagonist XAC decreased ERK activation by high concentrations of NECA, but modestly increased ERK activation in control conditions and in response to 1 and 10 nM NECA. In contrast, PD98059 did not alter CREB, whereas both H-89 and XAC blocked NECA-induced CREB activation. These data indicate that NECA results in ERK activation independent of the cAMP response;

10 **FIG. 6** shows both Enprofylline and JW V-108 antagonize activation of p42 and p44 ERK/MAP kinase by NECA. HRECs were serum-starved for 24 hr and pre-treated with adenosine deaminase (ADA, 1 U/mL) for 20 min, incubated with the antagonists in the presence of ADA for 10 min. NECA (1 nM-10 μ M, 10 min) was used to activate ERK. ERK activation was analyzed by Western blot using the E10 monoclonal antibody, which recognizes the phosphorylated (active) form of the enzyme;

15 **FIG. 7A**, **FIG. 7B** and **FIG. 7C** show a schematic representation (FIG. 7A) of the A_{2B} adenosine receptor ribozyme showing the nucleotide sequence of the recognition arms (SEQ ID NO:1), as well as the complementary sequence of the synthetic target (SEQ ID NO:2). Cleavage of this target by the ribozyme is shown in the autoradiogram (FIG. 7B), demonstrating the cleavage kinetics. Band densities of cleaved vs. intact target were plotted as percent cleaved (FIG. 7C). The A_{2B} receptor ribozyme cleaves nearly 90% of target in a 1:1 molar ratio by 60 min;

20 **FIG. 8A** and **FIG. 8B** show A_{2B} adenosine receptor ribozyme reduces NECA-stimulated VEGF synthesis and cell proliferation in HREC. Cells were stimulated with 10 μ mol/L NECA alone (◆), or NECA plus 1 μ mol/L of either a mixed 37-mer oligoribonucleotide (sham, ■) or A_{2B} ribozyme (▲). Both the amount of VEGF secreted into the medium (top) and the degree of proliferation (bottom) were decreased by the ribozyme, and not by the sham oligonucleotide control; and

25 **FIG. 9** shows adenosine receptor antagonists reduce the degree of retinal neovascularization in the mouse pup model of oxygen-induced retinopathy. Daily IP injections of antagonists (30 mg/Kg body weight) resulted in a 54% to 70% reduction compared to untreated controls. The

number of eyes examined for each condition was at least 16. *Significantly different (p< 0.05) from uninjected.

5 **FIG. 10** shows the number of neovascular nuclei counted per eye section for both the uninjected and AAV-IGF1R Rz1 injected eyes. Helex IV is at least 6 bases in length. The underlined bases can be any RNA tetraloop of the form $^5\text{GNRA}^3$ or UUCG, where N is any nucleotide and R is G or A. N can be any ribonucleotide (A, C, G or U) and N' is the complementary nucleotide. Y is a pyrimidine. H is any nucleotide but guanosine (A, C or U). B is any nucleotide but adenine (G, C or U). V is the complement of B (G, C or A).

10 **FIG. 11** shows a schematic illustration of a representative hairpin ribozyme molecule of the present invention (SEQ ID NO:105, SEQ ID NO:106). In particular, FIG. 11 shows a general hammerhead ribozyme structure. The italicized positions are constant. The stem may be any 4 or 5 base double stranded helix with a $^5\text{G-C}^3$ base pair at the top of the stem as drawn. Helix IV is at least 6 bases in length. The underlined bases can be any RNA tetraloop of the form $^5\text{GNRA}^3$ or UUCG, where N is any nucleotide and R is G or A. N can be any ribonucleotide (A, C, G or & and 15 N' is the complementary nucleotide. Y is a pyrimidine. H is any nucleotide but guanosine (A, C or U). B is any nucleotide but adenine (G, C or U). V is the complement of B (G, C or A).

15 **FIG. 12** shows a schematic illustration of a representative hammerhead ribozyme molecule of the present invention (SEQ ID NO:107). The sequences of the arms may vary, as shown in Tables 4-8. The italicized positions are constant. The stem may be any 4 or 5 base double stranded helix with a $^5\text{G-C}^3$ base pair at the top of the stem as drawn. Underlined nucleotides in loop may be 20 $^5\text{UUCG}^3$ or $^5\text{GNRA}^3$, where N is any nucleotide and R is a purine nucleotide.

5.2.4 ADENOSINE A_{2B} RECEPTOR REQUIRED FOR HREC ERK ACTIVATION

NECA (1 nmol/L – 10 μ mol/L) induced a transient activation of ERK which peaked at 5 min and desensitized within 20 min. The rate of desensitization was dependent on NECA concentration since higher doses of NECA produced a more rapid desensitization (FIGS. 3A-3B).
5 The A₁-selective agonist CPA was also capable of stimulating ERK (FIGS. 4A-4C), however the A_{2A}-selective agonist CGS did not activate ERK. In order to determine the intracellular signaling pathways activated by NECA that regulate ERK activity, we pretreated cells for 30 min with the ERK/MPAK kinase (MEK) inhibitor PD98059 or the PKA inhibitor H-89 and stimulated with NECA for 5 min. PD98059 abolished ERK activation, while H-89 increased basal ERK activation
10 (FIG. 5). H-89 did not block NECA-stimulated ERK activation, suggesting that PKA is not involved in signaling from the adenosine receptor to ERK. The non-selective adenosine receptor antagonist XAC decreased ERK activation by high concentrations of NECA, but modestly increased ERK activation in control conditions and in response to 1 and 10 nM NECA. Interestingly, prolonged activation with NECA in the presence of XAC or SCH and CPX reduced
15 the rate of ERK desensitization, suggesting that adenosine receptors are involved in both activation and desensitization of ERK.

Phosphorylation of cAMP response element binding protein (CREB) at Ser¹³³ was examined following NECA stimulation in order to determine whether activation of cAMP pathways by NECA occurred independently of ERK activation. Cells were pretreated with PD98059 or H-89 and assayed for active CREB by western blot. PD98059 did not alter CREB activation, however both H-89 and XAC blocked CREB phosphorylation. These data indicate that ERK activation by NECA occurs independently of the cAMP response (FIG. 5).

Enprofylline and JW V108 exhibit greater selectivity for the A_{2B} receptor. Cells were pre-treated with both antagonists for 10 min and stimulated with increasing concentrations of NECA. Enprofylline completely abolished ERK activation, while JW V108 inhibited ERK activation at all concentrations except for 10 μ M. These data suggest that ERK activation occurs through both the A_{2B} and A₁ receptors, but not the A_{2A} receptor (FIG. 6). These data support a role for adenosine in the activation of ERK that may then induce the phosphorylation of HIF 1- α .

5.3 EXAMPLE 3 – DEVELOPMENT AND TESTING OF RIBOZYME TARGETING A_{2B} ADENOSINE RECEPTOR mRNA

The cleavage site of the A_{2B} antisense, between nucleotides 183 and 184, was demonstrated to be accessible within the secondary structure of the native mRNA by the antisense studies. A hammerhead ribozyme designed to cleave this message was then synthesized along with a 14-nucleotide target sequence (FIG. 7A). This target was end-labeled in a standard kinase reaction with ³²P, then incubated along with ribozyme (1:1 molar ratio) for 1, 2, 3, 4, 5, 10, 30, 60, 120 and 180 min. Nearly 90% of target was cleaved by 60 min (FIG. 7C), demonstrating the efficacy and rapid action of this ribozyme in a cell-free assay system. The ribozyme's effects on HREC proliferation and VEGF synthesis in response to adenosine receptor activation was examined. HRECs were plated in serum-free medium overnight to adhere and make them quiescent. Unattached cells were then removed by washing with Hank's balanced salt solution (HBSS). The cells were then incubated with 1 U/mL adenosine deaminase (ADA) for 20 min, after which was added either medium alone, 1 μmol/L A_{2B} receptor ribozyme, or 1 μmol/L of a synthetic mixed oligonucleotide of the same length as the ribozyme, all of which contained 10 μmol/L NECA. Cells were then incubated for a total of seven days. Sampling occurred every 24 hr as follows. Conditioned medium was collected and stored at -70°C until the end of the assay, after which it was analyzed for VEGF using a commercially available ELISA. The cells were enzymatically dissociated from the wells and counted using a Coulter counter. These latter results were then used to normalize the VEGF data to a constant cell number. FIGS. 8A-8B show that cells treated with ribozyme express up to 60% less VEGF protein in response to NECA than do either untreated cells or cells treated with sham oligonucleotide. Similarly, these same cells exhibited a 50% reduction in proliferation 7 days after NECA stimulation when exposed to ribozyme compared to control.

TABLE 4
ILLUSTRATIVE HAIRPIN RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
5	<u>Cleavage site</u>		
HelixII			
Helix I			
	↓		
ROD OPSIN mRNA-SPECIFIC:			
P23L target:	acgc a gcc	ucuuucg-3'	SEQ ID NO:3
Ribozyme arms:	ugcg aaga	agaaggc-5'	SEQ ID NO:108
F45L target:	aca u g guu	cugcug	SEQ ID NO:4
Ribozyme arms:	ugug aaga	gacgac	SEQ ID NO:109
G51A target:	ugcu g gcc	uucccc	SEQ ID NO:5
Ribozyme arms:	acgg aaga	aagggg	SEQ ID NO:110
G51G target:	ugcu g guc	uucccc	SEQ ID NO:6
Ribozyme arms:	acgg aaga	aagggg	SEQ ID NO:111
P53R target:	gcug g gcu	uccggc	SEQ ID NO:7
Ribozyme arms:	cgac aaga	aggccg	SEQ ID NO:112

	Q64stop target:	ucac c guc	uagcac	SEQ ID NO:8	Macke <i>et al.</i> , 1993
	Ribozyme arms:	agug aaga	aucug	SEQ ID NO:113	
	G90D target:	agg u g gcu	ucaccca	SEQ ID NO:9	Sieving <i>et al.</i> , 1992
5	Ribozyme arms:	uccg aaga	aguggu	SEQ ID NO:114	
	G106W target:	uucu g gcc	ccacag	SEQ ID NO:10	Sung <i>et al.</i> , 1991
	Ribozyme arms:	aagg aaga	gguguc	SEQ ID NO:115	
	G114D target:	ugga g gac	uucuuu	SEQ ID NO:11	Vaithinathan <i>et al.</i> , 1994
10	Ribozyme arms:	accu aaga	aagaaa	SEQ ID NO:116	
	R135L target:	aucg a guu	guacgu	SEQ ID NO:12	Jacobson <i>et al.</i> , 1991
	Ribozyme arms:	uagc aaga	caugca	SEQ ID NO:117	
15					
	R135P target:	aucg a gcc	guacgu	SEQ ID NO:13	Rodriguez <i>et al.</i> , 1993
	Ribozyme arms:	uagc aaga	caugca	SEQ ID NO:118	
	P180A target:	acau c gcc	gagggc	SEQ ID NO:14	Daiger <i>et al.</i> , 1995
20	Ribozyme arms:	ugug aaga	cucccg	SEQ ID NO:119	

	D190G target:	aauc	g gcu	acuaca	SEQ ID NO:15	Dryja et al., 1991
	Ribozyme arms:	uuag	aaga	ugaugu	SEQ ID NO:120	
	H211R target:	ucgu	g guc	cgcuuc	SEQ ID NO:16	Macke et al., 1993
5	Ribozyme arms:	aggcg	aaga	gcgaag	SEQ ID NO:121	
	H211P target:	ucgu	g guc	cccuuc	SEQ ID NO:17	Macke et al., 1993
	Ribozyme arms:	aggcg	aaga	gggaag	SEQ ID NO:122	
	F220C target:	cauc	u guu	ucugcu	SEQ ID NO:18	Bunge et al., 1993
	Ribozyme arms:	guagg	aaga	agacgaa	SEQ ID NO:123	
10	P347S target:	aggua	g gcc	ucggcc	SEQ ID NO:19	Dryja et al., 1990
	Ribozyme arms:	ucccg	aaga	agccgg	SEQ ID NO:124	

TABLE 5
ILLUSTRATIVE HAMMERHEAD RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
5	Target reads 5' to 3' ribozyme reads 3' to 5'		
	Rod Opsin mRNA-SPECIFIC:		
	P23H target: gccacuu cgagua	SEQ ID NO:20	Berson <i>et al.</i> , 1991
	ribozyme arms: cgguga gcucau	SEQ ID NO:125	
10			
	P23L target: gccucuu cgagua	SEQ ID NO:21	Dryja <i>et al.</i> , 1991
	ribozyme arms: cggaga gcucau	SEQ ID NO:126	
	Q28H target: cacacua cuaccu	SEQ ID NO:22	Bunge <i>et al.</i> , 1993
	ribozyme arms: guguga gagggaa	SEQ ID NO:127	
15			
	F45L target: augguuuc ugcuuga	SEQ ID NO:23	Sung <i>et al.</i> , 1991
	ribozyme arms: uaccaa acgacu	SEQ ID NO:128	
	L46R target: auguuuu ggcuuga	SEQ ID NO:24	Rodriguez <i>et al.</i> , 1993
	ribozyme arms: uacaaa ccgacu	SEQ ID NO:129	
20			

	G51R target:	uggccuu ccccau	SEQ ID NO:25	Dryja et al., 1992
	ribozyme arms:	acgca gggua	SEQ ID NO:130	
	G51A target:	uggccuu ccccau	SEQ ID NO:26	Macke et al., 1993
5	ribozyme arms:	accgg a gggua	SEQ ID NO:131	
	G51V target:	uggccuu ccccau	SEQ ID NO:27	Dryja et al., 1991
	ribozyme arms:	accaga gggua	SEQ ID NO:132	
10	P53R target:	uggccuu ccgcau	SEQ ID NO:28	Inglehearn et al., 1992
	ribozyme arms:	accga ggcguu	SEQ ID NO:133	
	T58R target:	cuuuccu agguc	SEQ ID NO:29	Bunge et al., 1993
	ribozyme arms:	gaagg a uccgag	SEQ ID NO:134	
15				
	T58R target:	caggcuc uacguc	SEQ ID NO:30	Bunge et al., 1993
	ribozyme arms:	guccga augcag	SEQ ID NO:135	
	Q64stop target:	caccguc uagcac	SEQ ID NO:31	Macke et al., 1993
20	ribozyme arms:	guggca aucgug	SEQ ID NO:136	

Q64stop target:	ccgucua gcacaa	SEQ ID NO:32	Macke et al., 1993
ribozyme arms:	ggcaga cguuu	SEQ ID NO:137	
)68-71 target:	ugaaacua cauccu	SEQ ID NO:33	Keen et al., 1991
ribozyme arms:	acuuga guagga	SEQ ID NO:138	
V87D target:	ggaccua gguggc	SEQ ID NO:34	Sung et al., 1991
ribozyme arms:	ccugga ccacccg	SEQ ID NO:139	
G90D target:	gugacuu caccag	SEQ ID NO:35	Sieving et al., 1992
ribozyme arms:	cacuga gugguc	SEQ ID NO:140	
G106W target:	cguuuuc ugcccc	SEQ ID NO:36	Sung et al., 1991
ribozyme arms:	gcagaa accggg	SEQ ID NO:141	
C110Y target:	caggaua caauuu	SEQ ID NO:37	Dryja et al., 1992
ribozyme arms:	guccua guuaaa	SEQ ID NO:142	
G114D target:	aggacuu cuuugg	SEQ ID NO:38	Vaithinathan et al., 1994
ribozyme arms:	uccuga gaaacg	SEQ ID NO:143	

5	R135G target: ribozyme arms:	aggggua cguggu ucccca gcacca	SEQ ID NO:39 SEQ ID NO:144	Bunge <i>et al.</i> , 1993
10	R135L target: ribozyme arms:	aguuggua cguggu ucacca gcacca	SEQ ID NO:40 SEQ ID NO:145	Andreasson <i>et al.</i> , 1992
15	R135P target: ribozyme arms:	aguuugua cguggu ucaaca gcacca	SEQ ID NO:41 SEQ ID NO:146	Jacobson <i>et al.</i> , 1991
20	P171L target: ribozyme arms:	agccgua cguggu ucggca gcacca	SEQ ID NO:42 SEQ ID NO:147	Rodriguez <i>et al.</i> , 1993
	C140S target: ribozyme arms:	ugguguc uaaggcc accaca auucgg	SEQ ID NO:43 SEQ ID NO:148	Macke <i>et al.</i> , 1993
	P171L target: ribozyme arms:	accccua cucggcc uggggaa gagcgg	SEQ ID NO:44 SEQ ID NO:149	Dryja <i>et al.</i> , 1991
	P171L target: ribozyme arms:	ccuacuc gccccg ggauuga cggccg	SEQ ID NO:45 SEQ ID NO:150	Dryja <i>et al.</i> , 1991

5	P171S target: ribozyme arms:	cacc <u>cuc</u> acucgc gugg <u>gga</u> ugaggc	SEQ ID NO:46 SEQ ID NO:151	Stone et al., 1993
10	Y178C target: ribozyme arms:	gug <u>cauc</u> cccgag cac <u>qua</u> gggcuc	SEQ ID NO:47 SEQ ID NO:152	Farrar et al., 1991
15	P180A target: ribozyme arms:	guac <u>auc</u> gccgag cau <u>qua</u> cggcuc	SEQ ID NO:48 SEQ ID NO:153	Daiger et al., 1995
20	C187Y target: ribozyme arms:	gc <u>ucqua</u> ugaaau cg <u>aggca</u> accuu <u>a</u>	SEQ ID NO:49 SEQ ID NO:154	Nathans et al., 1993
	G188R target: ribozyme arms:	uc <u>ququa</u> gaaucg ag <u>caca</u> cuu <u>aggc</u>	SEQ ID NO:50 SEQ ID NO:155	Dryja et al., 1991
	D190G target: ribozyme arms:	ug <u>gaauc</u> gg <u>cuac</u> ac <u>cuua</u> cc <u>gaug</u>	SEQ ID NO:51 SEQ ID NO:156	Dryja et al., 1991
	D190Y target: ribozyme arms:	gaa <u>ucua</u> cu <u>acua</u> cu <u>uaga</u> ga <u>ugau</u>	SEQ ID NO:52 SEQ ID NO:157	Fishman et al., 1992

	M207R target: ribozyme arms:	cagguuuc gugguc guccaa caccag	SEQ ID NO:53 SEQ ID NO:158	Farrar et al., 1992
5	H211R target: ribozyme arms:	cgugguc cggcuuc gcacca gcgaaag	SEQ ID NO:54 SEQ ID NO:159	Macke et al., 1993
10	H211P target: ribozyme arms:	cgugguc cccuuuc gcacca gggaaag	SEQ ID NO:55 SEQ ID NO:160	Macke et al., 1993
15	C264X target: ribozyme arms:	ccugaauc ugggug ggacuuua acccac	SEQ ID NO:56 SEQ ID NO:161	Vaithinathan et al., 1993
20	P267L target: ribozyme arms:	ggugcuc uacggcc ccacga augcgg	SEQ ID NO:57 SEQ ID NO:162	Fishman et al., 1992
	F220C target: ribozyme arms:	uaucauc ugguuuc auaguua acaaaag	SEQ ID NO:58 SEQ ID NO:163	Bunge et al., 1993
	F220C target: ribozyme arms:	cuguuuc ugcuau gacaaaa acgaua	SEQ ID NO:59 SEQ ID NO:164	Bunge et al., 1993

C222R target:	ucuuuuc	cgcuau	SEQ ID NO:60	Bunge <i>et al.</i> , 1993
ribozyme arms:	agacaa	gcgaua	SEQ ID NO:165	
A292E target:	agaguuuc	uuugcc	SEQ ID NO:61	Dryja <i>et al.</i> , 1993
ribozyme arms:	5 ucucaa	aaacgg	SEQ ID NO:166	
Q344stop target:	cgagcua	gguggc	SEQ ID NO:62	Sung <i>et al.</i> , 1991
ribozyme arms:	9 gcucga	ccaccu	SEQ ID NO:167	
P347S target:	uggccuc	ggccua	SEQ ID NO:63	Dryja <i>et al.</i> , 1990
ribozyme arms:	10 accgga	ccggau	SEQ ID NO:168	
RP1 mRNA-SPECIFIC:				
R677stop target:	aaaaaauc	uugaca	SEQ ID NO:64	Pierce <i>et al.</i> , 1999
ribozyme arms:	15 uuuuuua	aacugu	SEQ ID NO:169	
RDS/PERIPHERIN mRNA-SPECIFIC:				
C118 target:	ggcucuc	ugcuuuuc	SEQ ID NO:65	Farrar <i>et al.</i> , 1991
ribozyme arms:	20 ccgaga	acgaaag	SEQ ID NO:170	
R172Q target:	gguuuuuc	aggacu	SEQ ID NO:66	Wells <i>et al.</i> , 1993
ribozyme arms:	ccaaaa	uccuga	SEQ ID NO:171	

	R172W target: ribozyme arms:	gguuuuu gggacu ccaaaaa cccuga	SEQ ID NO:67 SEQ ID NO:172	Wells et al., 1993
5	P210R target: ribozyme arms:	guccguu ucagcu caggca agucga	SEQ ID NO:68 SEQ ID NO:173	Jackson et al., 1993
	C214S target: ribozyme arms:	gcuggcuc caaucc cgacga guuagg	SEQ ID NO:69 SEQ ID NO:174	Keen and Inglehearn, 1996
10	P216L target: ribozyme arms:	aauuuua gcuucgc uuagaa cgagca	SEQ ID NO:70 SEQ ID NO:175	Kajiwara et al., 1991
	P219 target: ribozyme arms:	cuaggcuc gggccc gaucga cggccgg	SEQ ID NO:71 SEQ ID NO:176	Kajiwara et al., 1991
15				

TABLE 6
ADDITIONAL ILLUSTRATIVE HAIRPIN RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
5	<u>Cleavage site</u>		
	HelixII ↓ Helix I		
	↓		
RDS/PERIPHERIN mRNA-SPECIFIC:			
C118 target:	ucuc u gcu	uucugc	SEQ ID NO: 72
Ribozyme arms:	agag aaga	aagacg	SEQ ID NO: 177
R172W target:	caac g guu	uuuggg	SEQ ID NO: 73
Ribozyme arms:	guug aaga	aaaccc	SEQ ID NO: 178
P210R target:	cgu c guu	ucagcu	SEQ ID NO: 74
Ribozyme arms:	gcag aaga	agucga	SEQ ID NO: 179
C214S target:	cagc u gcu	ccaauc	SEQ ID NO: 75
Ribozyme arms:	gucg aaga	gguuag	SEQ ID NO: 180
P216L target:	ucuu a gcu	cgcac	SEQ ID NO: 76
Ribozyme arms:	agag aaga	gcggug	SEQ ID NO: 181

P219 target : uccu a gcu cgcgcc
 Ribozyme arms : aggg aaga gcggccg
 SEQ ID NO:77
 SEQ ID NO:182
 Kajiwara et al., 1991